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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/979,539 | 11/20/2001 | Ira Pastan | 15280-3951US | 5936 |

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| EXAMINER | |
|---|---|
| BLANCHARD, DAVID J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/979,539 | PASTAN ET AL. | |
| | Examiner | Art Unit | |
| | David J Blanchard | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *6/15/2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *41-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40 and 51-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-66 are pending.

Claims 1, 21-22, 27, 33, 35 and 40 have been amended.

Claims 51-66 have been added.

Claims 41-50 remain withdrawn as being drawn to a nonelected invention.

2. Claims 1-40 and 51-66 are under examination.

3. The Examiner notes that newly added claims 56-68 were not numbered consecutively and have been renumbered as claims 54-66 in accordance with Rule 1.126. See MPEP 37 C.F.R. 1.126.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

***Objections/Rejections Withdrawn***

6. The objections to the specification, parts a-d, are withdrawn in view of Applicant's arguments and amendments to the specification.

7. The rejections of claims 1-40, parts a and b, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in view of the amendments to the claims.

8. The rejection of claims 8-11 under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make or use the invention commensurate in scope with the claim is withdrawn withdrawn upon further consideration as claims 8-11 are drawn to antibodies that contain both a heavy and a light chain (i.e., Fv, Fab, ect).

9. The rejection of claims 21 (part b) under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claim is withdrawn in view of Applicant's arguments and amendment to the claim.

10. The rejection of claims 1-5, 8, 10, 21, 27 and 31 under 35 U.S.C. 102(b) as being anticipated by over Yelton et al is withdrawn in view of Applicant's arguments and amendments to the claims.

11. The rejection of claims 1-5, 8, 10, 12-14, 16, 21, 27 and 31 under 35 U.S.C. 102(e) as being anticipated by over Marks et al is withdrawn in view of Applicant's arguments and amendments to the claims.

12. The rejection of claims 1 and 4 under 35 U.S.C. 102(b) as being anticipated by over Goyenechea et al is withdrawn in view of Applicant's arguments.

13. The rejection of claims 1-6, 8-21, 27-28, 31-34, 36-37 and 39-40 under 35 U.S.C. 103(a) as being unpatentable over Yelton et al in view of Chowdhury et al [a] and Chowdhury et al [b] is withdrawn in view of Applicant's arguments and amendments to the claims.

14. The rejection of claims 1-6, 8-21, 27-28, 31-34, 36-37 and 39-40 under 35 U.S.C. 103(a) as being unpatentable over Marks et al in view of Chowdhury et al [a] and

Chowdhury et al [b] is withdrawn in view of Applicant's arguments and amendments to the claims.

15. The rejection of claims 1-6, 8-21, 27-28, 31-34, 36-37 and 39-40 under 35 U.S.C. 103(a) as being unpatentable over Chowdhury et al [a] in view of Goyenechea et al and Adams et al and Marks et al is withdrawn in view of Applicant's arguments and amendments to the claims.

***Response to Arguments***

16. The rejection of claims 6, 7, 11, 17-20, 22-26, 35 and newly added claims 51-62 and 64-66 under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is MAINTAINED.

The response filed 6/15/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that Figure 1 of the specification sets forth the sequence of the variable heavy and light chains (Fvs) of the SS antibody and cites Goldsby et al for support as teaching that the hypervariable regions form the antibody binding site of the antibody molecule and therefore, Figure 1 provides all the information needed by a person of skill in the art to make the polypeptides claimed. In response to this argument the claims are drawn to the complete SS antibody and not just the variable heavy and light chains, thus, Applicant's arguments are not commensurate in

scope with the claimed invention. Figure 1 does not provide any information about the CH1, CH2, CH3 or the hinge region, which are all part of a complete antibody and therefore, the practitioner does not have all the information necessary to make and use the invention commensurate in scope with the claims. The response also directs the Examiner to MPEP 2173.02, which instructs the Examining Corps that claim language "must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing ordinary level skill in the pertinent art at the time the invention was made. In response to this argument the relevant text in the MPEP (2173.02) cited by Applicant is directed to 35 U.S.C. 112, second paragraph, an dhas no bearing on the instant rejection, which is made under 35 U.S.C. 112, first paragraph, enablement. Again, without the complete SS antibody to which the claims are drawn, the skilled artisan would not be able to make and use the instant SS antibody without undue experimentation.

17. The rejection of claims 1-7, 12-40 and newly added claims 51-55 and 57-66 under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims is MAINTAINED.

The response filed 6/15/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that the rejection is based on the unsupported assertion that both chains of an antibody are needed to make an intact antigen binding-site. Applicant provides Kuan and Pastan as evidence that an immunotoxin comprising only a VH domain could successfully target immunoconjugates to target cells. Further, the response argues that claim 19 of U.S. Patent 5,980,895 is drawn to a single chain immunotoxin targeted by either a VH chain without the presence of a VL chain, or a VL chain without the presence of a VH chain and thus, the Patent and Trademark Offcie has already officially recognized that a single chain of an antibody can be used as the targeting portion of an immunoconjugate. With respect to U.S. Patent 5,980,895, the Examiner does not know the prosecution history of the 895 patent and will not comment on the 895 patent or the prosecution history of this application. In response to Applicant's other arguments, the Examiner points out that the instant claims are drawn to a polypeptide comprising a mutated antibody heavy chain variable region or light chain variable region, the polypeptide having at least five times higher binding affinity for an antigen than does the parental antibody. While it appears that the Kuan and Pastan reference teaches a single chain immunotoxin that binds antigen, the Kuan and Pastan reference does not teach that the single-chain immunotoxin comprising only a VH domain binds antigen with at least five times greater affinity relative to a parental antibody or how the skilled artisan would mutate the heavy chain variable region to produce a polypeptide comprising a mutated antibody heavy chain variable region that binds antigen with at least five times greater affinity as compared to the parental

antibody commensurate in scope with the instant claims. In contrast, Kuan and Pastan teach that the single chain immunotoxin exhibited 10-fold lower binding affinity as compared to a dsFv-immunotxin, which comprises both VH and VL domains (see page 977, left column). Additionally, Kuan and Pastan do not teach any polypeptide comprising only a mutated antibody light chain variable region that binds antigen or binds antigen with at least five times higher binding affinity as compared to the parental antibody commensurate in scope with the instant claims. Finally, Kuan and Pastan appears to be contradictory in that Kuan and Pastan at page 974, left column, admit that Fv fragments, which contain both a VH and VL domain are the smallest functional modules of antibodies. Again, while it appears that Kuan and Pastan teach a single chain immunotoxin that binds antigen albeit with reduced affinity, this is the exception and not the norm in the antibody art. It is reiterated that the overwhelming body of literature supports that an intact antigen-binding site results from the association of a VH chain with a VL chain in their proper order and in the context of framework sequences which maintain their required conformation, forming a functional antigen binding site. Therefore, Kuan and Pastan do not enable a polypeptide having only a antibody heavy chain variable region or only a light chain variable region or a nucleic acid encoding said polypeptide or a method of killing a malignant cell with said polypeptide commensurate in scope with the claims.

18. The rejection of claims 1-6, 8-21, 27-28, 31-34, 36-37 and 39-40 and newly added claims 51-54, 56-61, 63-64 and 66 under 35 U.S.C. 103(a) as being

unpatentable over Chowdhury et al [a] in view of Wagner et al and Pastan et al and Adams et al is MAINTAINED.

The response filed 6/15/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that the combination of Chowdhury et al [a] and Wagner does not teach or suggest the present invention. The response argues that Wagner et al does not teach or suggest that an antibody that has already undergone the multiple rounds of phage display selection for affinity as taught by Chowdhury et al [a] can have its affinity further improved by mutation at hot spots recited in the claims. The response goes on to argue that Pastan et al and Adams et al do not make up for this deficiency, that is further improving the affinity of the SS antibody by mutation at hot spot motifs after the antibody had already undergone multiple rounds of phage display selection. In response to this argument, the Examiner clarifies that the combination of the references relied upon was not based on the mutation of hot spot motifs following affinity selection by phage display. The following is reiterated for Applicant's convenience. Chowdhury et al [a] teach that anti-mesothelin antibodies were not useful because of low affinity and poor internalization and a high affinity SS scFv-PE38 immunotoxin kills mesothelin expressing cells and produced regressions of mesothelin-containing tumors and Wagner et al teaches the consensus sequence [A/G, G, C/T, A/T] as a preferred target for mutation and most hot spots are associated with AGY serine codons and biased serine codon usage in immunoglobulins has evolved to help the somatic hypermutation machinery target CDRs and thus, mutations are targeted to residues that could yield increased affinity and away from sites that are more likely to

destroy the structural scaffolding. Thus, the skilled artisan at the time the invention was made to have been motivated to only mutate CDR hot spots in the SS antibody in order to increase the affinity of the SS antibody without screening large and multiple antibody phage libraries, avoid deleterious mutations in the structural scaffold of the antibody, and one would have been motivated to do so because Chowdhury et al [a] teach a high affinity SS scFv-PE38 immunotoxin that killed mesothelin expressing cells and produced regressions of mesothelin-containing tumors and Pastan et al teach anti-mesothelin antibodies for targeting cytotoxins such as pseudomonas endotoxin, diptheria toxin, ricin and abrin to mesothelin expressing cells and Adams et al teach that increased affinity leads to improved selective tumor delivery of scFv antibodies. Therefore the skilled artisan would have been motivated to increase the affinity of the SS scFv-PE38 by targeting mutations only to hot spot motifs having the consensus sequence [A/G, G, C/T, A/T] or AGY as a more efficient method for increasing the affinity of the antibody SS scFv-PE38 rather than by affinity selection, which requires screening large and multiple antibody phage libraries, and does not avoid deleterious mutations in the structural scaffold of the antibody because Chowdhury et al [a] teaches that a high affinity SS scFv-PE38 immunotoxin kills mesothelin expressing cells and produced regressions of mesothelin-containing tumors and Wagner et al teaches that the consensus sequence [A/G, G, C/T, A/T] is a preferred target for mutation and most hot spots are associated with AGY serine codons and biased serine codon usage in immunoglobulins has evolved to help the somatic hypermutation machinery target

CDRs and thus, mutations are targeted to residues that could yield increased affinity and away from sites that are more likely to destroy the structural scaffolding.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

***New Grounds of Rejections***

19. Claims 1-21, 27-29 and 33-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-21, 27-29 and 33-40 are indefinite for reciting "binding affinity for an antigen bound by a parental antibody" in claims 1, 27 and 33. Does the polypeptide comprising the mutated antibody heavy chain variable region or light chain variable region bind the antigen already bound to the parental antibody or does the mutated antibody bind the antigen with at least five times higher affinity relative to the parental antibody's affinity for said antigen?

20 Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The amendment to claim 21 has introduced NEW MATTER into the claim. The response filed 6/15/2004 states that support for the amendment to claim 21 can be found at page 29, lines 3-5, however apparent support for the broad limitation "expressed in conjunction with a surface protein of a bacteriophage". The specification at page 29, lines 3-5 only discloses that the scFv nucleic acid sequences (i.e., VH and VL chains) are fused in frame with gene III, which encodes the gIIIp of the filamentous phage. The specification does not provide support for the broader limitation of a polypeptide comprising a heavy chain variable region or light chain variable region expressed in conjunction with just any surface protein of a bacteriophage. Applicant is required to provide support for all limitations in the claim in the specification as originally filed or remove then from the claim.

***Conclusions***

21. No claim is allowed.

22. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER